REMARKS

A. Status of the Claims

Claims 1-27 were pending at the time of the Action. Claims 2-5 and 7 have been canceled. Claim 1 has been amended. Claim 1 has been amended to incorporate limitations from canceled claims 2, 5, and 7, and to replace the term "PCR" with "polymerase chain reaction," and to clarify that the amount of AC133 amplification product in the sample comprising cells of the subject is compared to "a non-cancer, control sample of peripheral blood mononuclear cells." Claims 15-27 are withdrawn pursuant to a restriction requirement. Thus, claims 1, 6, and 8-14 are under examination and stand rejected under 35 U.S.C. §112, first paragraph and §112, second paragraph. The specific grounds for rejection, and Applicants' response thereto, are set out in detail below.

B. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1, 2 and 5-14 were rejected as lacking an enabling disclosure. Applicants traverse this rejection.

The enablement rejection appears to be based on the following six characterizations of the specification presented on page 4 of the Action:

(a) the cells examined in the specification were not cancer cells, but mononuclear cells from cancer-affected and cancer-free individuals;

(b) there are no examples that that expression of AC133 is elevated in cancer cells of individuals affected with any other type of cancer;

(c) there is no evidence that expression of AC133 is elevated in cancer cells of individuals affected with any type of cancer;

(d) there is no evidence that the level of AC133 expression is correlated with tumor burden;

(e) there is no evidence that the level of AC133 expression is correlated with tumor relapse;

(f) there is no evidence that AC133 in mononuclear cells is elevated only in cases of cancer.

Applicants address each of items (a) through (f) below.

1. Items (a) and (c)

In items (a) and (c), the Action asserts that the working examples in the present specification are not enabling because AC133 expression was studied in mononuclear cells and not in cancer cells. The Action also cites publications by Singh *et al.*, Vercauteren *et al.*, and Lee *et al.* as evidence that AC133 is not expressed in human brain tumors, AML, and AML and ALL, respectively (Action, p. 5).

The currently claimed invention does not rely on the detection of AC133 in cancer cells as asserted in the Action. Rather, cancer diagnosis according to the currently claimed invention involves the detection of tumor angiogenic activity. Tumors cannot grow beyond a certain size without inducing the growth of new blood vessels (angiogenesis) to provide oxygen and other essential nutrients to the growing tumor. As described in the specification, mobilization of endothelial progenitor cells (EPCs) to the sites of angiogenesis is a hallmark of angiogenic activity (p. 8, ln. 12-13). Thus, assessing EPC levels provides a method for monitoring tumor angiogenic activity. Because AC133 expression is highly specific to EPCs (Specification, p. 8, ln. 7-9), the detection of AC133 transcripts in a cell sample can be used to estimate the number of EPCs in the sample, whereby an increase in the amount of AC133 transcripts in the sample, as compared to the amount of AC133 transcripts in a control (*e.g.,* a cell sample from another subject that does not have cancer), indicates angiogenic activity in the subject and, hence, that the subject has cancer.

Current claim 1 specifies that the sample is a peripheral blood sample and that RNA transcripts from peripheral blood mononuclear cells are obtained. Thus, the Action's arguments that the specification is not enabling because AC133 expression was studied in mononuclear cells and not in cancer cells, and that there are no examples of AC133 expression in any cancer cells, are not relevant to the enablement of the current claims.

2. Item (b)

In item (b), the Action asserts that there are no examples demonstrating that expression of AC133 is elevated in mononuclear cells of individuals affected with any other type of cancer. However, the currently claimed invention does not rely on the detection of any particular type of cancer cells. As explained above, cancer diagnosis according to the currently claimed invention involves the detection of tumor angiogenic activity.

As described in Example 3, AC133 mRNA was assayed in the peripheral blood of 58 colorectal cancer (CRC) patients and 10 healthy volunteers. AC133 was significantly higher in the peripheral blood of active CRC patients compared to that of the healthy volunteers. This study demonstrated that real time Q RT-PCR of AC133 correlated with the tumor status as a result of the underlying tumor angiogenesis and can be used as a surrogate marker of tumor angiogenesis (Specification, p. 31, ln. 12-14).

3. Items (d) and (e)

In items (d) and (e), the Action asserts that there is no evidence that the level of AC133 expression is correlated with tumor burden, and that there is no evidence that the level of AC133 expression is correlated with tumor relapse.

As described in the present specification, assessing EPC recruitment and proliferation may be used not only in identifying angiogenic activity of cancer, but also may be used for cancer prognosis, identifying angiogenic potential or background of early or metastatic cancer, assessing tumor burden, predicting tumor recurrence, assessing chemotherapy success, and

measuring remission (Specification, p. 9, ln. 9-15). In Example 2, two of the three CRC patients had metastatic disease, whereas the third patient had the primary tumor resected approximately 4 weeks previously, and showed a lower level AC133 as well as plasma VEGF level (Specification, p. 29, ln. 3-8 and FIG. 1). This data indicates that a decrease in tumor burden (surgery) is associated with decreased peripheral blood EPCs (Specification, p. 29, ln. 8-9).

In Example 3 in the present specification, real-time Q-RT-PCR of AC133 were performed in patients with or without active CRC (n = 44). The estimated median value of AC133 marker was significantly higher in patients with clinical disease (4.2; range: 0.017-106.9) as compared to those with no clinical disease (0.0017, range, 0.0-9.51); p value < 0.001 (Mann-Whitney test). When three median AC133 values (0.01, 0.05, 0.1), were used as cut-off points to estimate the odds ratio (OR) and 95% confidence interval (CI) distinguishing active or inactive radiographic disease status, all three points had statistically significant OR ranging from 8.2 – 14.6. Thus, the study in Example 3 showed that real time Q RT-PCR of AC133 correlated with the tumor status as a result of the underlying tumor angiogenesis.

Thus, the evidence shows that assessing EPC recruitment and proliferation via AC133 expression may be used for predicting tumor burden or predicting tumor recurrence.

4. Item (f)

In item (f), the Action asserts that there is no evidence that AC133 in mononuclear cells is elevated only in cases of cancer. The Action cites publications by Gill *et al.* and Nakatani *et al.* as evidence that there is an increase in the number of AC133-expressing cells in the blood of patients with vascular trauma and Kawasaki disease, respectively (Action, p. 5). Thus, the Action argues that conditions other than cancer may be the cause of elevated levels of AC133.

As discussed above, AC133 expression is highly specific to EPCs, thus the detection of AC133 transcripts in a cell sample can be used to estimate the number of EPCs in the sample. As described in the present specification, EPCs are thought to play a role in postnatal

angiogenesis and angiogenesis following vascular trauma (*e.g.,* burns, mechanical disruption) in addition to their involvement in cancer angiogenesis (Specification, p. 9, ln. 3-9). Thus, while the number of EPCs in a sample may be increased by postnatal angiogenesis or vascular trauma, such events are generally readily apparent to those in the art and will be taken into consideration For example, in the study population described in Example 3 of the specification patients with underlying active wound, inflammation, infection, surgery within the past 4 weeks, recent heart attack or stroke, or limb ischemia were not eligible (Specification, 29, ln 25-27). The specific details of how a medical practitioner examines a patient does not need to be included in the claims – such routine operating parameters are best left to the specification. *Ex parte Jackson*, 217 U.S.P.Q. 804 (CCPA 1982).

5. Conclusion

In view of the above, Applicants submit that the present specification contains a description sufficient to enable one skilled in the art to make and use the claimed invention without unduly extensive experimentation. The claims, therefore, are enabled.

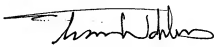
C. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1, 2 and 5-14 are rejected as allegedly indefinite over the use of trademarked materials in claim 1. An amendment has been provided removing the trademarked information. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this submission, a telephone call to the undersigned attorneyat (512) 536-5654 is invited.

Respectfully submitted,



Travis M. Wohlers
Reg. No. 57,423
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-5654

Date: September 19, 2006